REMARKS

Claim Amendments

Claims 1 and 31 are pending in the instant application. Claim 31 has been amended herein to recite a composition. Support for the amendments can be found throughout the specification and in the claims as originally filed. No new matter has been added.

Priority

The specification is amended herein to include a reference to the prior provisional application to which priority is claimed in the instant application. Applicants note that a reference to the prior application was first included with the Application Data Sheet filed with the application on January 14, 2004, and the priority claim was recognized by the Office as shown by its inclusion on the first filing receipt. Therefore, a petition under 37 C.F.R. 1.78(a) and the surcharge under 37 C.F.R. 1.17(t) are not required.

Objections to the Specification

Applicants will address the objections to the disclosure in the order presented in the Office Action.

A) The disclosure is objection to because the listing of references in the specification is not a proper information disclosure statement. Applicants note that an Information Disclosure Statement (IDS) and 1449 Form were filed with the USPTO listing all the references cited in the specification and were considered by the Examiner on January 22, 2007. Reconsideration and withdrawal of the objection are respectfully requested.

B) Tables 16, 18 and 19 have been amended herein to correlate the particular CpG oligonucleotide number with a respective SEQ ID NO. Reconsideration and withdrawal of the objection are respectfully requested.

C) The specification has been amended herein to include the correct address for the ATCC. Reconsideration and withdrawal of the objection are respectfully requested.

Provisional obviousness-type double patenting

Claims 1 and 31 are provisionally rejected over various claims of copending Application Nos. 10/279,684; 10/361,111; 11/153,054; and 11/174,002.

As stated by the Examiner, this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. If this provisional double patenting rejection is the only remaining rejection in the application, Applicants request that the Examiner withdraw the rejection and allow the application to issue as a patent (See MPEP §804(I)(B)). Applicants will then consider filing a Terminal Disclaimer or take any other action deemed necessary in the later filed copending applications.

Rejection of Claims 1 and 31 Under 35 U.S.C. §112, First Paragraph

Claims 1 and 31 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The office action states that the structure of the oligonucleotides that comprise the immunomer is not shown. Applicants respectfully disagree.

At page 5 of the specification, lines 9-13, the immunomer is described as "comprising at least two oligonucleotides linked at their 3' ends, an internucleotide linkage, or a functionalized nucleobase or sugar via a non-nucleotidic linker, at least one of the oligonucleotides being an immunostimulatory oligonucleotide and having an accessible 5' end."

Each limitation of this description is either defined in the specification, or has a well-recognized meaning in the art, or both. Looking at each limitation separately, the written description is as follows:

"**comprising**": This term has a well-recognized meaning in the art. The transitional term 'comprising' (and other comparable terms, *e.g.*, 'containing,' 'including,' and 'having') is 'open-ended--it covers the expressly recited subject matter, alone or in combination with unrecited subject matter. *See, e.g.,* *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) (' "Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.'); *Ex parte Davis*, 80 USPQ 448, 450 (Patent Off. Bd. App. 1948) ('comprising' leaves the 'claim open for the inclusion of unspecified ingredients even in major amounts').

"**at least two**": Applicants respectfully submit that one skilled in the art would recognize this to mean two or more, with no upper limit. Since the number of oligonucleotides is not relevant to the invention, as long as there are at least two, this is an adequate description.

"**oligonucleotides**": Applicants respectfully submit that the term "oligonucleotide" has a well-recognized meaning in the art, and would not confuse one skilled in the art as to its meaning. Moreover, the specification defines this term at page 16, line 17, through page 17, line 27:

> For purposes of the invention, the term "oligonucleotide" refers to a polynucleoside formed from a plurality of linked nucleoside units. Such oligonucleotides can be obtained from existing nucleic acid sources, including genomic or cDNA, but are preferably produced by synthetic methods. In preferred embodiments each nucleoside unit includes a heterocyclic base and a pentofuranosyl, trehalose, arabinose, 2'-deoxy-2'-substituted arabinose, 2'-O-substituted arabinose or hexose sugar group. The nucleoside residues can be coupled to each other by any of the numerous known internucleoside linkages. Such internucleoside linkages include, without limitation, phosphodiester, phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboalkoxy, acetamidate, carbamate, morpholino, borano, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate, and sulfone internucleoside linkages. The term "oligonucleotide" also encompasses polynucleosides having one or more stereospecific internucleoside linkage (e.g., (R_P)- or (S_P)-phosphorothioate, alkylphosphonate, or phosphotriester linkages). As used herein, the terms "oligonucleotide" and "dinucleotide" are expressly intended to include polynucleosides and dinucleosides having any such internucleoside linkage, whether or not the linkage comprises a phosphate group. In certain preferred embodiments, these internucleoside linkages may be phosphodiester, phosphorothioate, or phosphorodithioate linkages, or combinations thereof.
>
> In some embodiments, the oligonucleotides each have from about 3 to about 35 nucleoside residues, preferably from about 4 to about 30 nucleoside residues, more preferably from about 4 to about 20 nucleoside residues. In some embodiments, the immunomers comprise oligonucleotides have from about 5 to about 18, or from about 5 to about 14, nucleoside residues. As used herein, the term "about" implies that the exact number is not critical. Thus, the number of nucleoside residues in the oligonucleotides is not critical, and oligonucleotides having one or two fewer nucleoside residues, or from one to several additional nucleoside residues are contemplated as equivalents of each of the embodiments described above. In some embodiments, one or more of the oligonucleotides have 11 nucleotides. In the context of immunostimulatory oligonucleotides, preferred embodiments have from about 13 to about 35 nucleotides, more preferably from about 13 to about 26 nucleotides.

> The term "oligonucleotide" also encompasses polynucleosides having additional substituents including, without limitation, protein groups, lipophilic groups, intercalating agents, diamines, folic acid, cholesterol and adamantane. The term "oligonucleotide" also encompasses any other nucleobase containing polymer, including, without limitation, peptide nucleic acids (PNA), peptide nucleic acids with phosphate groups (PHONA), locked nucleic acids (LNA), morpholino-backbone oligonucleotides , and oligonucleotides having backbone sections with alkyl linkers or amino linkers.

Since, within this description, the precise nature of the oligonucleotide is not relevant to the invention, this is an adequate written description.

"**linked at their 3' ends, an internucleotide linkage, or a functionalized nucleobase or sugar**": Each of these terms has a well-recognized meaning in the art. Moreover, representative structures implicated in this term are shown in the specification at Figure 13.

"**via a non-nucleotidic linker**": This term is defined, as well as exemplified, in the specification at page 29, line 6 through page 31, line 14.

> For purposes of the invention, a "non-nucleotidic linker" is any moiety that can be linked to the oligonucleotides by way of covalent or non-covalent linkages. Preferably such linker is from about 2 angstroms to about 200 angstroms in length. Several examples of preferred linkers are set forth below. Non-covalent linkages include, but are not limited to, electrostatic interaction, hydrophobic interactions, π-stacking interactions, and hydrogen bonding. The term "non-nucleotidic linker" is not meant to refer to an internucleoside linkage, as described above, e.g., a phosphodiester, phosphorothioate, or phosphorodithioate functional group, that directly connects the 3'-hydroxyl groups of two nucleosides. For purposes of this invention, such a direct 3'-3' linkage (no linker involved) is considered to be a "nucleotidic linkage."
>
> In some embodiments, the non-nucleotidic linker is a metal, including, without limitation, gold particles. In some other embodiments, the non-nucleotidic linker is a soluble or insoluble biodegradable polymer bead.
>
> In yet other embodiments, the non-nucleotidic linker is an organic moiety having functional groups that permit attachment to the oligonucleotide. Such attachment preferably is by any stable covalent linkage. As a non-limiting example, the linker may be attached to any suitable position on the nucleoside, as illustrated in Figure 13. In some preferred embodiments, the linker is attached to the 3'-hydroxyl. In such embodiments, the linker preferably comprises a hydroxyl functional group, which preferably is attached to the 3'-hydroxyl by means of a

phosphodiester, phosphorothioate, phosphorodithioate or non-phosphate-based linkages.

In some embodiments, the non-nucleotidic linker is a biomolecule, including, without limitation, polypeptides, antibodies, lipids, antigens, allergens, and oligosaccharides. In some other embodiments, the non-nucleotidic linker is a small molecule. For purposes of the invention, a small molecule is an organic moiety having a molecular weight of less than 1,000 Da. In some embodiments, the small molecule has a molecular weight of less than 750 Da.

In some embodiments, the small molecule is an aliphatic or aromatic hydrocarbon, either of which optionally can include, either in the linear chain connecting the oligonucleotides or appended to it, one or more functional groups selected from the group consisting of hydroxy, amino, thiol, thioether, ether, amide, thioamide, ester, urea, and thiourea. The small molecule can be cyclic or acyclic. Examples of small molecule linkers include, but are not limited to, amino acids, carbohydrates, cyclodextrins, adamantane, cholesterol, haptens and antibiotics. However, for purposes of describing the non-nucleotidic linker, the term "small molecule" is not intended to include a nucleoside.

In some embodiments, the small molecule linker is glycerol or a glycerol homolog of the formula $HO\text{-}(CH_2)_o\text{-}CH(OH)\text{-}(CH_2)_p\text{-}OH$, wherein o and p independently are integers from 1 to about 6, from 1 to about 4, or from 1 to about 3. In some other embodiments, the small molecule linker is a derivative of 1,3-diamino-2-hydroxypropane. Some such derivatives have the formula $HO\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH_2\text{-}CH(OH)\text{-}CH_2\text{-}NHC(O)\text{-}(CH_2)_m\text{-}OH$, wherein m is an integer from 0 to about 10, from 0 to about 6, from 2 to about 6, or from 2 to about 4.

Some non-nucleotidic linkers according to the invention permit attachment of more than two oligonucleotides, as schematically depicted in Figure 1. For example, the small molecule linker glycerol has three hydroxyl groups to which oligonucleotides may be covalently attached. Some immunomers according to the invention, therefore, comprise more than two oligonucleotides linked at their 3' ends to a non-nucleotidic linker. Some such immunomers comprise at least two immunostimulatory oligonucleotides, each having an accessible 5' end.

Thus, the specification contains a written description of a non-nucleotidic linker.

"**at least one of the oligonucleotides being an immunostimulatory oligonucleotide**": The term "at least one" requires no further clarification. Nor does the term "being".

The term "an immunostimulatory oligonucleotide" is defined and exemplified at various points in the specification, both functionally and structurally, including:

page 19, line 10 through page 20, line 10:

For purposes of the invention, the term "immunostimulatory oligonucleotide" refers to an oligonucleotide as described above that induces an immune response when administered to a vertebrate, such as a fish, fowl, or mammal. As used herein, the term "mammal" includes, without limitation rats, mice, cats, dogs, horses, cattle, cows, pigs, rabbits, non-human primates, and humans. Useful immunostimulatory oligonucleotides can be found described in Agrawal *et al.*, WO 98/49288, published November 5, 1998; WO 01/12804, published February 22, 2001; WO 01/55370, published August 2, 2001; PCT/US01/13682, filed April 30, 2001; and PCT/US01/30137, filed September 26, 2001. Preferably, the immunomodulatory oligonucleotide comprises at least one phosphodiester, phosphorothioate, or phosphorodithioate internucleoside linkage.

In some embodiments, the immunomodulatory oligonucleotide comprises an immunostimulatory dinucleotide of formula 5'-Pyr-Pur-3', wherein Pyr is a natural or synthetic pyrimidine nucleoside and Pur is a natural or synthetic purine nucleoside. In some preferred embodiments, the immunomodulatory oligonucleotide comprises an immunostimulatory dinucleotide of formula 5'-Pur*-Pur-3', wherein Pur* is a synthetic purine nucleoside and Pur is a natural or synthetic purine nucleoside. In various places the dinucleotide is expressed as RpG, C*pG or YZ, in which case respectively, R, C*, or Y represents a synthetic purine. A particularly preferred synthetic purine is 2-oxo-7-deaza-8-methyl-purine. When this synthetic purine is in the Pur* position of the dinucleotide, species-specificity (sequence dependence) of the immunostimulatory effect is overcome and cytokine profile is improved. As used herein, the term "pyrimidine nucleoside" refers to a nucleoside wherein the base component of the nucleoside is a monocyclic nucleobase. Similarly, the term "purine nucleoside" refers to a nucleoside wherein the base component of the nucleoside is a bicyclic nucleobase. For purposes of the invention, a "synthetic" pyrimidine or purine nucleoside includes a non-naturally occurring pyrimidine or purine base, a non-naturally occurring sugar moiety, or a combination thereof.

The immunostimulatory dinucleotides now recited in amended claim 37 are described in the specification at page 23, lines 9-18:

In preferred embodiments, the immunostimulatory dinucleotide is selected from the group consisting of CpG, C*pG, CpG*, and C*pG*, wherein the base of C is cytosine, the base of C* is 2'-thymine, 5-hydroxycytosine, N4-alkyl-cytosine, 4-thiouracil or other non-natural pyrimidine, or 2-oxo-7-deaza-8-methylpurine, wherein when the base is 2-oxo-7-deaza-8-methyl-purine, it is preferably covalently bound to the 1'-position of a pentose via the 1 position of the base; the base of G is guanosine, the base of G* is 2-amino-6-oxo-7-deazapurine, 2-oxo-7-deaza-8-methylpurine, 6-thioguanine, 6-oxopurine, or other non-natural purine nucleoside, and p is an

internucleoside linkage selected from the group consisting of phosphodiester, phosphorothioate, and phosphorodithioate.

"**having an accessible 5' end**": This term is defined in the specification at page 12, line 26 through page 13, line 5.

> As used herein, the term "accessible 5' end" means that the 5' end of the oligonucleotide is sufficiently available such that the factors that recognize and bind to immunomers and stimulate the immune system have access to it. In oligonucleotides having an accessible 5' end, the 5' OH position of the terminal sugar is not covalently linked to more than two nucleoside residues or any other moiety that interferes with interaction with the 5' end. Optionally, the 5' OH can be linked to a phosphate, phosphorothioate, or phosphorodithioate moiety, an aromatic or aliphatic linker, cholesterol, or another entity which does not interfere with accessibility.

The term "comprising" does not vitiate written description.

The office action states that the "structure of the immunomer (at least two oligonucleotides) is vast in view of the recitation of the open claim language of 'comprising'." However, as described in item 1, above, this term is an accepted transitional term in patent claims. Thus, its use does not affect the written description requirement.

The cited case law is not relevant to the instant claims.

Applicants note that several cases are cited in the office action in support of this rejection, in particular *Fujikawa v. Wattanasin*, *In re Ruschig*, *Purdue Pharma L.P. v. Faulding Inc.* and *Ex parte Ohshiro*. Each of these cases is inapposite to the rejection of the present claims. In each of those cases, a genus was disclosed in the specification, but the claim was directed to a species or subgenus that was not disclosed in the specification. That is not the case for the present claims. The present claims are all literally supported in the language of the specification as filed.

The remaining cases cited, namely *Fiers v. Revel* and *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, merely stand for the proposition that written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, a point which Applicants do not contest, but which does not describe the written description for claims 37, 39-40 and 42-60.

The Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, paragraph 1, 'Written Description' Requirement (66 FR 1099-1111, January, 5, 2001 lack the force of law, but at any rate, are consistent with the present written description.

In the office action, reference is made to "The Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, paragraph 1, 'Written Description' Requirement (66 FR 1099-1111, January, 5, 2001." (hereafter "The Guidelines"). Of course, this latter reference does not have the force or effect of law, as described in its own preamble:

> These 'Written Description Guidelines' are intended to assist Office personnel in the examination of patent applications for compliance with the written description requirement of 35 §112, P 1. This revision is based on the Office's current understanding of the law and public comments received in response to the USPTO's previous request for public comments on its Revised Interim Written Description Guidelines and is believed to be fully consistent with binding precedent of the U.S. Supreme Court, as well as the U.S. Court of Appeals for the Federal Circuit and its predecessor courts. This revision does not constitute substantive rulemaking and hence does not have the force and effect of law.

Id.

However, Applicants note that The Guidelines, with respect to generic claims, as at issue here, states:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice ..., reduction to drawings ..., or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
>
> A 'representative number of species' means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be situations where one species adequately supports a genus. What constitutes a 'representative number' is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. Description of a representative number of species does not require the description to be of such

specificity that it would provide individual support for each species that the genus embraces.

Applicants' specification provides written description according to these parameters. Tables 4B through 25D provide several examples of species of immunomers that fall within generic claims 1 and 31 and the use thereof. These species differ in size, oligonucleotide composition, immunostimulatory dinucleotide composition, and the nature of non-nucleotidic linkage. Moreover, several species of control oligonucleotides lacking specific components of the claimed immunomers are provided for comparative purposes. The comparisons show the effects of the various limitations of the claimed immunomers on their immune stimulatory capacity.

Thus, clearly this is not a case where a single species is relied upon to support an entire genus. These many species, actually reduced to practice and structurally defined in the specification fully meet the statement in the Guidelines that an adequate written description of the claimed invention must include sufficient description of at least a representative number of species. Moreover, these species demonstrate the functional requirements of the immunomer according to the invention, including the accessible 5' end, and the lack of a requirement of particular oligonucleotide sequences, with the exception of the immunostimulatory dinucleotide.

Neither the Guidelines, nor the relevant case law requires more. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1 and 31 Under 35 U.S.C. §112, First Paragraph

Claims 1 and 31 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Office Action states that the specification does not enable a pharmaceutical use for the claimed composition.

The Applicant, without conceding to the correctness of the position stated in the Office Action, but in order to expedite prosecution of the instant application, has removed the term "pharmaceutical" from the claims as suggest on page 20 of the Office Action. The Applicant reserves the right to prosecute the deleted subject matter at a later date or in a timely filed divisional application. The Applicant submits that the Examiner's rejection is rendered moot by

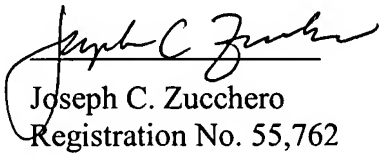
the withdrawal of this claim, and therefore, respectfully requests that the Examiner withdraw this objection.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

Dated: July 9, 2007

By: 

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